

Glycolytic enzyme Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH) and Neurological disorders

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Abstract

Glyceraldehyde 3-phosphate dehydrogenase (abbreviated as **GAPDH** or less commonly as GAPDH) (EC 1.2.1.12) is an enzyme of ~37kDa that catalyses the sixth step of glycolysis and thus serves to break down glucose for energy and carbon molecules. GAPDH initially identified as a glycolytic enzyme and considered as a housekeeping gene, is widely used as an internal control in experiments on proteins, mRNA, and DNA. GAPDH is encoded by a single gene on human chromosome 12 that gives rise to an individual mRNA transcript with no known splice variants. GAPDH is tightly regulated at transcriptional and posttranscriptional levels, which are involved in the regulation of diverse GAPDH functions. Several factors such as insulin, hypoxia inducible factor-1 (HIF-1), p53, nitric oxide (NO), and acetylated histone, not only modulate *GAPDH* gene expression but also affect protein functions via common pathways. Oxidoreductase GAPDH has become a subject of interest as studied revealed a surfeit of diverse GAPDH functions depending on its post-translational modifications (PTMs), extending beyond traditional aerobic metabolism of glucose. As a result of multiple isoforms, cellular locales and diverse functions, GAPDH is able to come in contact with a variety of small molecules, proteins, membranes, etc., that play important roles in normal and pathologic cell function. Specially, GAPDH has been implicated in several neurodegenerative diseases and disorders, largely through interactions with other proteins specific to that disease or disorder. For example, GAPDH interactions with beta-amyloid precursor protein (beta APP) could interfere with its function regarding the cytoskeleton or membrane transport and can cause Alzheimer disease (AD), while interactions with Huntington could interfere with its function regarding apoptosis, nuclear tRNA transport, DNA replication, and DNA repair. In addition, nuclear translocation of GAPDH has been reported in Parkinson's disease (PD), and several anti-apoptotic PD

drugs, such as rasagiline, function by preventing the nuclear translocation of GAPDH. In this review, recent findings related to GAPDH and Neurological disorder are summarized.

Introduction

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a glycolytic enzyme that is responsible for the sixth step of glycolysis¹. In addition to this metabolic function, GAPDH is now recognized as a multifunctional protein that exhibits other functions, including DNA repair², transcriptional and posttranscriptional gene regulation³, intracellular membrane trafficking⁴, and cell death^{5,6}. In GAPDH mediated cell death pathway, the involvement of GAPDH in nuclear translocation and its aggregation under oxidative stress have been proposed⁷⁻⁹. The active-site cysteine (Cys-152) seems to play a crucial role in both pathways. For example, GAPDH binds to Siah (seven in absentia homolog) through oxidation/S-nitrosylation of Cys-152 and translocate into the nucleus in response to oxidative stress, such as that from nitric oxide(NO)¹⁰. Nuclear GAPDH activates p300/CREB (cAMP-response element-binding protein)-binding protein (CBP)¹¹ and poly(ADP-ribose)polymerase-1¹². Additionally, oxidative stress or initiate amyloid-like GAPDH aggregation via intermolecular disulphide bond at Cys-152¹³⁻¹⁵.

The accumulation of unfolded proteins can cause protein aggregation in the aged brain, and these aggregates facilitate the formation of pathological amyloid deposits, which is a key cause of several neurodegenerative/neuropsychiatric disorders.

1. GAPDH and Alzheimer disease (AD)

Alzheimer disease (AD) is a progressive neurodegenerative disorder characterized by loss of neurons and formation of pathological extracellular deposits induced by amyloid- β peptide (A β)¹⁶. Numerous studies have established A β amyloidogenesis as a hallmark of AD pathogenesis¹⁷, particularly with respect to mitochondrial dysfunction. Some scientist have proven that glycolytic glyceraldehyde-3-phosphate dehydrogenase (GAPDH) forms amyloid-like aggregates upon exposure to oxidative stress¹⁸, and these aggregates contribute to neuronal cell death¹⁹. Aggregated GAPDH in the brain is also amyloidogenic, and GAPDH amyloid aggregates localize with Lowy bodies in Parkinson's disease and with senile plaques and neurofibrillary tangles in Alzheimer's disease²⁰.

It has been posited that abnormal protein aggregation leads to mitochondrial dysfunction²¹, proteasome inhibition²², endoplasmic reticulum (ER) stress²³, and autophagy²⁴, which

ultimately cause cell death. Notably, 5–20% of the total GAPDH under physiological conditions is generally bound to the mitochondria. Further, treatment of isolated mitochondria with GAPDH directly caused their dysfunction through the activation of voltage-dependent anion channels^{25,26}, which are known components of the mitochondrial permeability transition pore(PTP)²⁷. PTP opening leads to mitochondrial depolarization and the release of cell death mediators from the intermembrane space, such as cytochromes (cytc) and apoptosis-inducing factor (AIF)²⁸. From these observations, we focused on mitochondria to elucidate the neuronal cell death pathway that is mediated by GAPDH aggregation.

2. GAPDH and Huntington's disease

Huntington's disease (HD), is an autosomal, dominantly inherited, progressive neurodegenerative disease caused by CAG-trinucleotide repeat expansion (coding for a polyglutamine, polyQ, stretch) in the first exon of the gene IT15,²⁹ which encodes a large (~350 kDa) protein called huntingtin³⁰ and mutation in this gene leads to the production of an expanded polyglutamine stretch in the encoded protein³¹, affecting ~5–10 per 100,000 people in the Western world³². Mutant protein, huntingtin, likely affects a wide range of cellular pathways and functions by abnormally interacting with a variety of proteins and intracellular organelles, thus contributing to the pathology underlying HD³³. Patients affected by HD usually carry more than 35 repeats in their mutant huntingtin as compared to 16–20 repeats in the normal population³⁴.

After 10–20 years of onset of this disease, HD patients die due to complications from the disease³⁵. Although the mutation in the huntingtin gene was identified more than 20 years ago³⁶, only symptomatic management³⁷ is currently available to treat the disease. Thus, it is important to identify the molecular mechanisms leading to the pathology associated with mutant huntingtin in HD and develop therapeutics targeting them. Mitochondrial dysfunction has been implicated in the pathology of HD because neurons, with high-energy demands, are dependent on mitochondria as a source of energy production to maintain their functions³⁸.

The dynamin family of GTPases (guanosinetriphosphatases) regulate the constantly repeated process of fission and fusion due to which mitochondria actively move from the neuronal soma to the axon and dendrites³⁹. The mitochondria fission and fusion collectively referred to as dynamics, are significantly disturbed and imbalanced in HD⁴⁰ leading to accumulation of fragmented and damaged mitochondria which ultimately leads to oxidative stress in cells. The cycle of fusion and fission is very closely coordinated with mitochondrial autophagy or

mitophagy, a process of selective elimination of damaged mitochondria by autophagic machinery. Abnormalities at different phases of mitophagy in HD and in other neurodegenerative diseases have been proposed to contribute to disease progression through unknown mechanisms⁴¹.

A new form of micro-mitophagy in which GAPDH associates with damaged mitochondria under oxidative stress induced by ischemia–reperfusion injury in hearts and promotes direct uptake of damaged mitochondria into the lysosomal structure that is composed of hybrid organelles of lysosomes and late endosomes, has been identified by one of the group. This process of micro-mitophagy occurs independently of the catalytic/metabolic activity of GAPDH⁴². In their study they sought to explore whether and how this GAPDH-driven mitophagy is regulated in HD. GAPDH is identified as one such protein which interacts with/affected by mutant huntingtin. It is reported that expression of mutant huntingtin with expanded polyglutamine repeats negatively regulates GAPDH-driven mitophagy thus contributing to HD-associated pathology. HD associated pathology leading to accumulation of damaged mitochondria and inhibition of their removal by mitophagy suggests that it may also occur in other neurodegenerative diseases. Why macro-autophagy does not compensate for the impaired micro-autophagy it is still unclear. Whether GAPDH-mediated mitophagy is deployed together with a macro-autophagic pathway to remove damaged mitochondria and whether both pathways are impaired or inhibited with expression of mutant huntingtin with expanded polyglutamine repeats in HD are also unclear. GAPDH mediated mitophagy may also be incorporated into CMA, as Oxidized GAPDH is also a substrate of chaperone-mediated autophagy (CMA)^{43,44,45} but this process still remains to be elucidated. Thus a better understanding of its mechanism will help with the elimination of damaged mitochondria that will allow us to prevent or slow down the disease progression. Under oxidative stress caused by expression of mutant huntingtin, GAPDH translocates to damaged mitochondria, which is an initial step toward cytoprotective mitophagy. GAPDH at the outer mitochondrial membrane selectively associates with mutant huntingtin with expanded polyglutamine repeats, thereby blocking GAPDH mediated clearance of the damaged mitochondria by lysosomes⁴⁶. By over expressing catalytically inactive GAPDH (iGAPDH), this mutant huntingtin-induced impairment of mitophagy can be corrected; iGAPDH enhanced the blunted mitophagy and resulted in improved mitochondrial function and cell survival in cells expressing expanded polyglutamine repeats.

Micro-mitophagy provides a potential therapeutic approach to treat HD and maybe other neurodegenerative diseases as these data reflect a critical role of GAPDH-driven mitophagy in HD. But because of the complexity of the disease, a comprehensive treatment must also include a selective inhibitor of mitochondrial fission protein (Drp1) and a pharmacological activator of the macro-autophagic pathway such as mTOR-inhibiting drug rapamycin may provide the greatest therapeutic potential^{47,48,49}. Also, some of the work shows that some DNA aptamers which bound to the elongated polyglutamine stretch of huntingtin with high affinity inhibited the aggregation of the protein in vitro. These aptamers succeeded in decreasing membrane permeabilization with concomitant reduction in intracellular oxidative stress⁵⁰. They were also able to inhibit sequestration of an essential cellular enzyme, viz. GAPDH. Hence aptamers seems to be logical tool to slow down the progress of the disease by inhibiting the primary aggregation step.

3. GAPDH and Parkinson's disease (PD)

Parkinson's disease (PD) is a progressive age related neurodegenerative disorder with a prevalence of ~1% in people over 60years of age⁵¹. Pathologically it is characterized by the 1 together with the presence of proteinaceous cytoplasmic inclusions⁵². The majority of PD cases are apparently sporadic, while approximately 5–10% of the patients present an autosomal dominant or recessive mode of inheritance⁵³. The etiology of sporadic PD is complex and multifactorial, involving aging, genetic and environmental risk factors. Over the years, candidate gene association studies have been extensively employed to identify loci where common variants contribute to the risk of PD⁵⁴. Most recently a number of new susceptibility loci associated with PD have been identified through genome-wide association studies (GWAS)⁵⁵. It has been found that GAPDH and glycosaminoglycans (GAGs) are associated with α -SN amyloid aggregates in Parkinson disease^{56,57,58}. GAPDH has been seen to co-localize with α -SN in amyloid aggregates in post-mortem tissue of patients with sporadic Parkinson disease and promotes the formation of Lewy body-like inclusions in cell culture⁵⁹. Some recent data suggests that GADPH also possesses highly diverse non-glycolitic functions in the intra or extracellular space⁶⁰ and has also been related to neurodegenerative diseases. GAPDH has a protective effect on late-onset Alzheimer disease⁶¹ which has been suggested by genomic analysis. If not all but GAGs are present in mosttypes of amyloids inside and outside of the cells^{62,63}. Protein aggregation kinetics is affected by GAGs, which is proved in vivo⁶⁴. It has been reported recently that sulfated GAGs, like heparin and heparansulfates, are able to trigger GAPDH amyloid aggregation under pH and

temperature physiological conditions⁶⁵. The GAPDH species induced by heparin formed during the early stages of the aggregation process (HI-GAPDH_{ESS}) are able to accelerate α -SN aggregation with a higher efficiency⁶⁶. The interaction among GAGs, GAPDH, and α -SN exerts a protective role on dopaminergic cell survival⁶⁷.

GAPDH is critically involved in many other cellular processes including neurodegeneration apart from cellular energy metabolism. GAPDH protein plays an important role in dopaminergic neuronal apoptosis. GAPDH co-aggregates with α -synuclein which is the primary component of Lewy inclusion, which is confirmed from studies done on both cell models and post mortem brain tissues from sporadic PD. Abnormal aggregation and nuclear translocation of GAPDH protein were consistently observed in several in vitro apoptotic models induced by various neurotoxins including MPP, 6-OHDA and rotenone^{68,69}. Furthermore, once the GAPDH were knock-downed, reduced cytotoxicity of these neurotoxins on dopaminergic cells were seen importantly, a recent in-vitro study in SHY-SY5Y showed that substitution of cysteine for serine-284 of human GAPDH led to aggregate prone GAPDH, which resulted in greater oxidative stress linked cell death than expression of wild type-GAPDH⁷⁰. These findings suggest consistently that alteration in GAPDH function derived from genetic variation might be implicated in the pathogenesis of PD.

GAPDH is identified as a novel autoantigen that is expressed in neuronal cells at the plasma membrane level and is recognized by serum autoantibodies from patients affected with neurodegenerative disorder.⁷¹ Serum IgG immuno-reactivity to GAPDH was found in a high percentage of patients with major depression as compared to unaffected control individuals or patients with bipolar disorder⁷². Autoantibodies against GAPDH were also found in both the CSF and serum from patients with neuropsychiatric manifestations, suggesting that these antibodies, generated in the periphery, penetrate the CNS from the peripheral blood across the altered blood-brain barrier and bind to cell surfaces, possibly interfering with neuronal functions. GAPDH also has an important role in neurite outgrowth⁷³ which suggested that anti-GAPDH antibodies, when acting to block the binding of the molecule to laminin and/or to other adhesion and synaptic molecules in the CNS, may alter neuronal plasticity^{74,75}. In vivo administration of anti-GAPDH antibodies in C57BL6/J mice resulted in behavioral changes associated with a detrimental cognitive and emotional profile.

Current status

It is also investigated that the neuroprotective actions of deprenyl and TCH346 reflect their preventing GAPDH Siah binding and the nuclear translocation of GAPDH. It appears that the initial action of the drugs is to bind to GAPDH, as it is directly demonstrated binding of TCH346 to GAPDH⁷⁶. Such binding would inhibit S-nitrosylation of GAPDH and its binding to Siah. Recently it is observed that rasagiline, a monoamine oxidase inhibitor used in the therapy of PD, is also neuroprotective in multiple animal models and prevents the nuclear translocation of GAPDH⁷⁷. Although the principal focus for the therapeutic actions of deprenyl has been PD, deprenyl and related drugs might be useful in other neuronal conditions as well as non-nervous system conditions, because the GAPDH Siah cascade appears fairly universal^{78, 79, 80}. Thus a wide range of stressors in diverse cell lines elicits nuclear translocation of GAPDH with antisense to GAPDH preventing nuclear translocation and cell death. The most investigated GAPDH systems involve apoptotic death. Whether GAPDH plays a role in necrosis or in non-apoptotic programmed cell death is unclear. In addition to the therapeutic relevance, evidences supported cytoprotective actions of drugs involve blockade of the GAPDH Siah system provides support for the concept that the GAPDH Siah signalling cascade is an important component of cell death⁸¹.

GAPDH is a redox-sensitive protein whose activity is largely affected by oxidative modifications at its highly reactive cysteine residue in the enzyme's active site (Cys149). Prolonged exposure to oxidative stress may cause, inter alia, the formation of intermolecular disulfide bonds leading to accumulation of GAPDH aggregates and ultimately to cell death.

Using the model of oxidative stress based on SK-N-SH human neuroblastoma cells treated with hydrogen peroxide it is observed that down- or up-regulation of GAPDH content caused inhibition or enhancement of the protein aggregation and respectively reduced or increased the level of cell death. The ability of the compounds to bind GAPDH molecules was proved by the drug affinity responsive target stability assay, molecular docking and differential scanning calorimetry. Results of experiments with SK-N-SH human neuroblastoma treated with hydrogen peroxide showed that two substances, RX409 and RX426, lowered the degree of GAPDH aggregation and reduced cell death by 30%. Oxidative injury was emulated in vivo by injecting of malonic acid into the rat brain, and it was showed that the treatment with RX409 or RX426 inhibited GAPDH-mediated aggregation in the brain, reduced areas of the injury as proved by magnetic resonance imaging, and augmented the behavioral status of the

rats as established by the "beam walking" test. In conclusion, the data show that two GAPDH binders could be therapeutically relevant in the treatment of injuries stemming from hard oxidative stress⁸².

Novel evidences indicate that low molecular compounds may be effective inhibitors potentially preventing the GAPDH translocation to the nucleus, and inhibiting or slowing down its aggregation and oligomerization. Naturally occurring compound, piceatannol, to interact with GAPDH and to reveal its effect on functional properties and selected parameters of the dehydrogenase structure. The obtained data revealed that piceatannol binds to GAPDH. The ITC analysis indicated that one molecule of the tetrameric enzyme may bind up to 8 molecules of polyphenol (7.3 ± 0.9). Potential binding sites of piceatannol to the GAPDH molecule were analyzed using the Ligand Fit algorithm. Conducted analysis detected 11 ligand binding positions. It is indicated that piceatannol decreases GAPDH activity. Detailed analysis presume that this effect is due to piceatannol ability to assemble a covalent binding with nucleophilic cysteine residue (Cys149) which is directly involved in the catalytic reaction. Thus it is demonstrated that by binding with GAPDH piceatannol blocks cysteine residue and counteracts its oxidative modifications that induce oligomerization and GAPDH aggregation. Recently these anomalies have been linked with the pathogenesis of Alzheimer's disease⁸³.

Future Directions

GAPDH has become a subject of interest as studied revealed a surfeit of diverse GAPDH functions. As a result of multiple isoforms, cellular locales and diverse functions, GAPDH is able to come in contact with a variety of small molecules, proteins, membranes, etc., that play important roles in normal and pathologic cell function. Specially, GAPDH has been implicated in several neurodegenerative diseases and disorders, largely through interactions with other proteins specific to that disease or disorder. Various cell culture models have conclusively demonstrated that initiation of apoptosis by a variety of ways involves an increase in the nuclear expression of GAPDH. This increased nuclear expression is dependent on the synthesis of new GAPDH protein. Whereas some GAPDH translocation from the cytosol may occur, this appears to be on a small scale and results in the activation of GAPDH transcription. This new GAPDH protein appears to have novel characteristics and is nuclear targeted. This nuclear-targeted GAPDH then regulates transcription to initiate PCD cascades. There is now accumulating evidence that these observations may have relevance to human

neurodegenerative conditions. As such, recent reports have shown increased nuclear GAPDH associated with susceptible neurons in post-mortem samples from patients with a variety of neurodegenerative conditions. Small-molecule compounds with demonstrated anti-apoptotic activity that selectively interact with GAPDH have been identified. These compounds have also been shown to prevent the increase in nuclear GAPDH associated with the cell culture models in which they show anti-apoptotic activity. It is proposed that this effect is the result of binding to GAPDH, preventing the subsequent increase in GAPDH synthesis and nuclear accumulation. One of these compounds, CGP 3466, is currently undergoing Phase II clinical trials as a disease-modifying agent for Parkinson's disease, while others are in development. Thus, GAPDH may be used as an important therapeutic target in many neurological disorders like Parkinson disease, Alzheimer disease and Huntington's disease etc.

References

1. Tristan C, Shahani N, Sedlak TW, Sawa A. *The diverse functions of GAPDH: views from different subcellular compartments.* *Cell Signal.* 2011 Feb;23(2):317-23. doi: 10.1016/j.cellsig.2010.08.003. Epub 2010 Aug 19.
2. A. A. Kosova, S. N. Khodyreva and O. I. Lavrik. *Role of Glyceraldehyde3Phosphate Dehydrogenase (GAPDH) in DNA Repair.* ISSN 00062979, *Biochemistry (Moscow)*, 2017, Vol. 82, No. 6, pp. 643654. © Pleiades Publishing, Ltd., 2017.
3. Jin-Ying Zhang, Fan Zhang, Chao-Qun Hong, Armando E. Giuliano, Xiao-Jiang Cui, Guang-Ji Zhou, Guo-Jun Zhang, and Yu-Kun Cui. *Critical protein GAPDH and its regulatory mechanisms in cancer cells.* *Cancer Biol Med.* 2015 Mar; 12(1): 10–22.
4. Tisdale EJ, Kelly C, Artalejo CR. *Glyceraldehyde-3-phosphate dehydrogenase interacts with Rab2 and plays an essential role in endoplasmic reticulum to Golgi transport exclusive of its glycolytic activity.* *J Biol Chem.* 2004 Dec 24;279(52):54046-52. Epub 2004 Oct 14.
5. Anna Colell, Jean-Ehrland Ricci, Stephen Tait Sandra Milasta, Ulrich Maurer, Lisa Bouchier-Hayes, Patrick Fitzgerald, Ana Guio-Carrion, Nigel J. Waterhouse, Cindy Wei Li, Bernard Mari, Pascal Barbry, Donald D. Newmeyer, Helen M. Beere, and Douglas R. Green. *GAPDH and Autophagy Preserve Survival after Apoptotic Cytochrome c Release in the Absence of Caspase Activation.* *Cell.* Volume 129, Issue 5, 1 June 2007, Pages 983-997.
6. Colell A, Green DR, Ricci JE. *Novel roles for GAPDH in cell death and carcinogenesis.* *Cell Death Differ.* 2009 Dec;16(12):1573-81. doi: 10.1038/cdd.2009.137. Epub 2009 Sep 25.
7. Kusner LL, Sarthy VP, Mohr S. *Nuclear translocation of glyceraldehyde-3phosphate dehydrogenase: a role in high glucose-induced apoptosis in retinal Müller cells.* *Invest Ophthalmol Vis Sci.* 2004 May;45(5):1553-61
8. Ortiz-Ortiz MA, Morán JM, Ruiz-Mesa LM, Bravo-San Pedro JM, Fuentes JM. *Paraquat exposure induces nuclear translocation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and the activation of the nitric oxide-GAPDH-Siah cell death cascade.* *Toxicol Sci.* 2010 Aug;116(2):614-22. doi: 10.1093/toxsci/kfq146. Epub 2010 May 17.
9. Akira Sawa, Adil A. Khan, Lynda D. Hester, and Solomon H. Snyder. *Glyceraldehyde-3-phosphate dehydrogenase: Nuclear translocation participates in neuronal and non-neuronal cell death.* *Proc Natl Acad Sci U S A.* 1997 Oct 14; 94(21): 11669–11674.

10. Lee SY, Kim JH, Jung H, Chi SW, Chung SJ, Lee CK, Park BC, Bae KH, Park SG. *Glyceraldehyde-3-phosphate, a glycolytic intermediate, prevents cells from apoptosis by lowering S-nitrosylation of glyceraldehyde-3-phosphate dehydrogenase.* J MicrobiolBiotechnol. 2012 Apr;22(4):571-3.
11. Yego EC¹, Mohr S. *siah-1 Protein is necessary for high glucose-induced glyceraldehyde-3-phosphate dehydrogenase nuclear accumulation and cell death in Muller cells.* J Biol Chem. 2010 Jan 29;285(5):3181-90. doi: 10.1074/jbc.M109.083907. Epub 2009 Nov 23.
12. Nakajima H, Kubo T, Ihara H, Hikida T, Danjo T, Nakatsuji M, Shahani N, Itakura M, Ono Y, Azuma YT, Inui T, Kamiya A, Sawa A. *Nuclear-translocated Glyceraldehyde-3-phosphate Dehydrogenase Promotes Poly(ADP-ribose) Polymerase-1 Activation during Oxidative/Nitrosative Stress in Stroke.* J Biol Chem. 2015 Jun 5;290(23):14493-503. doi: 10.1074/jbc.M114.635607. Epub 2015 Apr 16.
13. Nakajima H, Amano W, Kubo T, Fukuhara A, Ihara H, Azuma YT, Tajima H, Inui T, Sawa A, Takeuchi T. *Glyceraldehyde-3-phosphate dehydrogenase aggregate formation participates in oxidative stress-induced cell death.* J Biol Chem. 2009 Dec 4;284(49):34331-41. doi: 10.1074/jbc.M109.027698. Epub 2009 Oct 16.
14. Nakajima H, Amano W, Fujita A, Fukuhara A, Azuma YT, Hata F, Inui T, Takeuchi T. *The active site cysteine of the proapoptotic protein glyceraldehyde-3-phosphate dehydrogenase is essential in oxidative stress-induced aggregation and cell death.* J Biol Chem. 2007 Sep 7;282(36):26562-74. Epub 2007 Jul 5.
15. Nakajima H, Itakura M, Kubo T, Kaneshige A, Harada N, Izawa T, Azuma YT, Kuwamura M, Yamaji R, Takeuchi T. *Glyceraldehyde-3-phosphate Dehydrogenase (GAPDH) Aggregation Causes Mitochondrial Dysfunction during Oxidative Stress-induced Cell Death.* J Biol Chem. 2017 Mar 17;292(11):4727-4742. doi: 10.1074/jbc.M116.759084. Epub 2017 Feb 6.
16. Matsui T, Ingelsson M, Fukumoto H, Ramasamy K, Kowa H, Frosch MP, Irizarry MC, Hyman BT. *Expression of APP pathway mRNAs and proteins in Alzheimer's disease.* Brain Res. 2007 Aug 3;1161:116-23. Epub 2007 Jun 5.
17. Itakura M, Nakajima H, Kubo T, Semi Y, Kume S, Higashida S, Kaneshige A, Kuwamura M, Harada N, Kita A, Azuma YT, Yamaji R, Inui T, Takeuchi T. *Glyceraldehyde-3-phosphate Dehydrogenase Aggregates Accelerate Amyloid-*

β Amyloidogenesis in Alzheimer Disease. J Biol Chem. 2015 Oct 23;290(43):26072-87. doi: 10.1074/jbc.M115.669291. Epub 2015 Sep 10.

18. Masanori Itakura, Hidemitsu Nakajima, Takeya Kubo, Yuko Semi, Satoshi Kume, Shusaku Higashida, Akihiro Kaneshige, Mitsuru Kuwamura, Naoki Harada, Akinori Kita, Yasu-Taka Azuma, Ryoichi Yamaji, Takashi Inui and Tadayoshi Takeuchi. *Glyceraldehyde-3-Phosphate Dehydrogenase Aggregates Accelerate Amyloid-β Amyloidogenesis in Alzheimer Disease* doi: 10.1074/jbc.M115.669291. jbc.M115.669291.
19. Nakajima H, Itakura M, Kubo T, Kaneshige A, Harada N, Izawa T, Azuma YT, Kuwamura M, Yamaji R, Takeuchi T. *Glyceraldehyde-3-phosphate Dehydrogenase (GAPDH) Aggregation Causes Mitochondrial Dysfunction during Oxidative Stress-induced Cell Death*. J Biol Chem. 2017 Mar 17;292(11):4727-4742. doi: 10.1074/jbc.M116.759084. Epub 2017 Feb 6.
20. Qin Wang, Randall L. Woltjer, P. J. Cimino, Catherine Pan, Kathleen S. Montine, Jing Zhang, and Thomas J. Montine. *Proteomic analysis of neurofibrillary tangles in Alzheimer disease identifies GAPDH as a detergent-insoluble paired helical filament tau binding protein*. The FASEB Journal express article 10.1096/fj.04-3210fj. March 2005.
21. Akbar M, Essa MM, Daradkeh G, Abdelmegeed MA, Choi Y, Mahmood L, Song BJ. *Mitochondrial dysfunction and cell death in neurodegenerative diseases through nitrooxidative stress*. Brain Res. 2016 Apr 15;1637:34-55. doi: 10.1016/j.brainres.2016.02.016. Epub 2016 Feb 13.
22. Ciechanover A, Kwon YT. *Protein Quality Control by Molecular Chaperones in Neurodegeneration*. Front Neurosci. 2017 Apr 6;11:185. doi: 10.3389/fnins.2017.00185. eCollection 2017.
23. Rammohan V Rao and Dale E Bredesen. *Misfolded proteins, endoplasmic reticulum stress and neurodegeneration*. Curr Opin Cell Biol. 2004 Dec; 16(6): 653–662.
24. Liu C1, Gao Y, Barrett J, Hu B. *Autophagy and protein aggregation after brain ischemia*. J Neurochem. 2010 Oct;115(1):68-78. doi: 10.1111/j.1471-4159.2010.06905.x. Epub 2010 Aug 12

25. Hidemitsu Nakajima, Masanori Itakura, Takeya Kubo, Akihiro Kaneshige, Naoki Harada, Takeshi Izawa, Yasu-Taka Azuma, Mitsuru Kuwamura, Ryouichi Yamaji, and Tadayoshi Takeuchi. *Glyceraldehyde-3-phosphate Dehydrogenase (GAPDH) Aggregation Causes Mitochondrial Dysfunction during Oxidative Stress-induced Cell Death* J Biol Chem. 2017 Mar 17; 292(11): 4727–4742.
26. Nakajima H, Amano W, Fukuhara A, Kubo T, Misaki S, Azuma YT, Inui T, Takeuchi T. *An aggregate-prone mutant of human glyceraldehyde-3-phosphate dehydrogenase augments oxidative stress-induced cell death in SH-SY5Y cells.* BiochemBiophys Res Commun. 2009 Dec 18;390(3):1066-71.
27. Nakajima H, Itakura M, Kubo T, Kaneshige A, Harada N, Izawa T, Azuma YT, Kuwamura M, Yamaji R, Takeuchi T. *Glyceraldehyde-3-phosphate Dehydrogenase (GAPDH) Aggregation Causes Mitochondrial Dysfunction during Oxidative Stress-induced Cell Death.* J Biol Chem. 2017 Mar 17;292(11):4727-4742. doi: 10.1074/jbc.M116.759084. Epub 2017 Feb 6.
28. Granville DJ, Cassidy BA, Ruehlmann DO, Choy JC, Brenner C, Kroemer G, van Breemen C, Margaron P, Hunt DW, McManus BM. *Mitochondrial release of apoptosis-inducing factor and cytochrome c during smooth muscle cell apoptosis.* Am J Pathol. 2001 Jul;159(1):305-11.
29. Elisabeth Möncke-Buchner Stefanie Reich Merlind Mücke Monika Reuter Walter Messer Erich E. Wanker Detlev H. Krüger. *Counting CAG repeats in the Huntington's disease gene by restriction endonuclease Eco P15I cleavage.* Nucleic Acids Research, Volume 30, Issue 16, 1 August 2002, Pages e83,
30. Zheng Z, Diamond MI. *Huntington disease and the huntingtin protein.* Prog Mol Biol Transl Sci. 2012;107:189-214. doi: 10.1016/B978-0-12-385883-2.00010-2.
31. Clabough EB, Zeitlin SO. *Deletion of the triplet repeat encoding polyglutamine within the mouse Huntington's disease gene results in subtle behavioral/motor phenotypes in vivo and elevated levels of ATP with cellular senescence in vitro.* Hum Mol Genet. 2006 Feb 15;15(4):607-23. Epub 2006 Jan 10.
32. Zheng S, Ghitani N, Blackburn JS, Liu JP, Zeitlin SO. *A series of N-terminal epitope tagged Hdh knock-in alleles expressing normal and mutant huntingtin: their application to understanding the effect of increasing the length of normal Huntingtin's polyglutamine stretch on CAG140 mouse model pathogenesis.* Mol Brain. 2012 Aug 14;5:28. doi: 10.1186/1756-6606-5-28.

33. Basu M, Bhattacharyya NP, Mohanty PK. *Comparison of modules of wild type and mutant Huntingtin and TP53 protein interaction networks: implications in biological processes and functions.* PLoS One. 2013 May 31;8(5):e64838. doi: 10.1371/journal.pone.0064838.
34. Jessica K. Lee, Amy Conrad, Eric Epping, Kathy Mathews, Vincent Magnotta, Jeffrey D. Dawson, and Peg Nopoulos. *Effect of Trinucleotide Repeats in the Huntington's Gene on Intelligence.* EBioMedicine. 2018 May; 31: 47–53.
35. Sánchez-Díaz G, Arias-Merino G, Villaverde-Hueso A, Morales-Piga A, Abaitua-Borda I, Hens M, Bermejo-Sánchez E, Posada de la Paz M, Alonso-Ferreira V. *Monitoring Huntington's Disease Mortality across a 30-Year Period: Geographic and Temporal Patterns.* Neuroepidemiology. 2016;47(3-4):155-163. doi: 10.1159/000452860. Epub 2016 Nov 25.
36. Jae WhanKeum, Aram Shin, Tammy Gillis, JayalakshmiSrinidhi Mysore, Kawther Abu Elneel, Diane Lucente, Tiffany Hadzi, Peter Holmans, Lesley Jones, Michael Orth, SeungKwak, Marcy E. MacDonald, James F. Gusella, and Jong-Min Lee. *The HTT CAG-Expansion Mutation Determines Age at Death but Not Disease Duration in Huntington Disease.* AJHG. Volume 98, Issue 2, 4 February 2016, Pages 287-298
37. Ross CA, Aylward EH, Wild EJ, Langbehn DR, Long JD, Warner JH, Scahill RI, Leavitt BR, Stout JC, Paulsen JS, Reilmann R, Unschuld PG, Wexler A, Margolis RL, Tabrizi SJ. *Huntington disease: natural history, biomarkers and prospects for therapeutics.* Nat Rev Neurol. 2014 Apr;10(4):204-16. doi:10.1038/nrneurol.2014.24. Epub 2014 Mar 11.
38. Silva AC, Almeida S, Laço M, Duarte AI, Domingues J, Oliveira CR, Januário C, Rego AC. *Mitochondrial respiratory chain complex activity and bioenergetic alterations in human platelets derived from pre-symptomatic and symptomatic Huntington's disease carriers.* Mitochondrion. 2013 Nov;13(6):801-9. doi: 10.1016/j.mito.2013.05.006. Epub 2013 May 23.
39. Song W, Chen J, Petrilli A, Liot G, Klinglmayr E, Zhou Y, Poquiz P, Tjong J, Pouladi MA, Hayden MR, Masliah E, Ellisman M, Rouiller I, Schwarzenbacher R, Bossy B, Perkins G, Bossy-Wetzel E. *Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity.* Nat Med. 2011 Mar;17(3):377-82. doi: 10.1038/nm.2313. Epub 2011 Feb 20.
40. Solesio ME, Saez-Atienzar S, Jordan J, Galindo MF. *3-Nitropropionic acid induces autophagy by forming mitochondrial permeability transition pores rather than*

activating the mitochondrial fission pathway. Br J Pharmacol. 2013 Jan;168(1):63-75. doi: 10.1111/j.1476-5381.2012.01994.x.

41. Martinez-Vicente M. *Neuronal Mitophagy in Neurodegenerative Diseases*. Front Mol Neurosci. 2017 Mar 8;10:64. doi: 10.3389/fnmol.2017.00064. eCollection 2017.
42. GouriYogalingam, Sunhee Hwang, Julio C. B. Ferreira, and DariaMochly-Rosen: *Glyceraldehyde-3-phosphate Dehydrogenase (GAPDH) Phosphorylation by Protein Kinase C δ (PKC δ) Inhibits Mitochondria Elimination by Lysosomal-like Structures following Ischemia and Reoxygenation-induced Injury* J Biol Chem. 2013 Jun 28; 288(26): 18947–18960.
43. Joan S Steffan. *Does Huntingtin play a role in selective macroautophagy?* Cell Cycle. 2010 Sep 1; 9(17): 3401–3413.
44. Mazzola JL, Sirover MA. *Alteration of nuclear glyceraldehyde-3-phosphate dehydrogenase structure in Huntington's disease fibroblasts*. Brain Res Mol Brain Res. 2002 Apr 30;100(1-2):95-101.
45. Sunhee Hwang, Marie-Hélène Disatnik, and DariaMochly-Rosen. *Impaired GAPDH-induced mitophagy contributes to the pathology of Huntington's disease*. EMBO Mol Med. 2015 Oct; 7(10): 1307–1326.
46. Senatorov VV, Charles V, Reddy PH, Tagle DA, Chuang DM. *Overexpression and nuclear accumulation of glyceraldehyde-3-phosphate dehydrogenase in a transgenic mouse model of Huntington's disease*. Mol Cell Neurosci. 2003 Mar; 22(3):285-97.
47. Maurizio Renna , Maria Jimenez-Sanchez , SovanSarkar, and David C. Rubinsztein. *Chemical Inducers of Autophagy That Enhance the Clearance of Mutant Proteins in Neurodegenerative Diseases*. Published, JBC Papers in Press, February 10, 2010, DOI 10.1074/jbc.R109.072181.
48. Martinez-Vicente M. *Autophagy in neurodegenerative diseases: From pathogenic dysfunction to therapeutic modulation*. Semin Cell Dev Biol. 2015 Apr;40:115-26. doi: 10.1016/j.semcdb.2015.03.005. Epub 2015 Apr 2.
49. Sarkar S. *Regulation of autophagy by mTOR-dependent and mTOR-independent pathways: autophagy dysfunction in neurodegenerative diseases and therapeutic*

application of autophagy enhancers. *Biochem Soc Trans*. 2013 Oct;41(5):1103-30. doi: 10.1042/BST20130134.

50. Baehyun Shin, Roy Jung, Hyejin Oh, Gwen E. Owens, Hyeongseok Lee, Seungkwak Ramee Lee, Susan L. Cotman, Jong-Min Lee, Marcy E. MacDonald, Ji-Joon Song, Ravi Vijayvargia, and Ilhn Sik Seong. *Novel DNA Aptamers that Bind to Mutant Huntingtin and Modify Its Activity*. *Mol Ther Nucleic Acids*. 2018 Jun 1; 11: 416–428.
51. Wong SL, Gilmour H, Ramage-Morin PL. *Parkinson's disease: Prevalence, diagnosis and impact*. *Health Rep*. 2014 Nov;25(11):10-4.
52. Winter C, von Rumohr A, Mundt A, Petrus D, Klein J, Lee T, Morgenstern R, Kupsch A, Juckel G. *Lesions of dopaminergic neurons in the substantia nigra pars compacta and in the ventral tegmental area enhance depressive-like behavior in rats*. *Behav Brain Res*. 2007 Dec 3;184(2):133-41. Epub 2007 Jul 7.
53. Claudia Schulte and Thomas Gasser. *Genetic basis of Parkinson's disease: inheritance, penetrance, and expression*. *Appl Clin Genet*. 2011; 4: 67–80.
54. Lynn M. Bekris, Ignacio F. Mata, and Cyrus P. Zabetian. *The Genetics of Parkinson Disease*. *J Geriatr Psychiatry Neurol*. 2010 Dec; 23(4): 228–242.
55. Towfique Raj, Joshua M. Shulman, Brendan T. Keenan, Lori B. Chibnik, Denis A. Evans, David A. Bennett, Barbara E. Stranger, and Philip L. De Jager. *Alzheimer Disease Susceptibility Loci: Evidence for a Protein Network under Natural Selection*. *Am J Hum Genet*. 2012 Apr 6; 90(4): 720–726.
56. Clarisa M. Torres-Bugeau, César L. Ávila, Rita Raisman-Vozari, Dulce Papy-Garcia, Rosangela Itri, Leandro R. S. Barbosa, Leonardo M. Cortez, Valerie L. Sim, and Rosana N. Chehín. *Characterization of Heparin-induced Glyceraldehyde-3-phosphate Dehydrogenase Early Amyloid-like Oligomers and Their Implication in α -Synuclein Aggregation*. *J Biol Chem*. 2012 Jan 20; 287(4): 2398–2409.
57. Ávila CL, Torres-Bugeau CM, Barbosa LR, Sales EM, Ouidja MO, Socías SB, Celej MS, Raisman-Vozari R, Papy-Garcia D, Itri R, Chehín RN. *Structural characterization of heparin-induced glyceraldehyde-3-phosphate dehydrogenase protofibrils preventing α -synuclein oligomeric species toxicity*. *J Biol Chem*. 2014 May 16;289(20):13838-50. doi: 10.1074/jbc.M113.544288. Epub 2014 Mar 26.

58. Sonia Lehari-Boufala, Mohand-Ouidir Ouidja, Véronique Barbier-Chassefière, Emilie Hénault, Rita Raisman-Vozari, Laure Garrigue-Antar, Dulce Papy-Garcia, and Christophe Morin. *New Roles of Glycosaminoglycans in α -Synuclein Aggregation in a Cellular Model of Parkinson Disease*. PLoS One. 2015; 10(1): e0116641.
59. Tsuchiya K1, Tajima H, Kuwae T, Takeshima T, Nakano T, Tanaka M, Sunaga K, Fukuhara Y, Nakashima K, Ohama E, Mochizuki H, Mizuno Y, Katsube N, Ishitani R. *Pro-apoptotic protein glyceraldehyde-3-phosphate dehydrogenase promotes the formation of Lewy body-like inclusions*. Eur J Neurosci. 2005 Jan;21(2):317-26.
60. Cortez LM, Avila CL, Bugeau CM, Fariás RN, Morero RD, Chehín RN. *Glyceraldehyde-3-phosphate dehydrogenase tetramer dissociation and amyloid fibril formation induced by negatively charged membranes*. FEBS Lett. 2010 Feb 5;584(3):625-30. doi: 10.1016/j.febslet.2009.12.012. Epub 2009 Dec 13.
61. Mazzola JL, Sirover MA. *Reduction of glyceraldehyde-3-phosphate dehydrogenase activity in Alzheimer's disease and in Huntington's disease fibroblasts*. J Neurochem. 2001 Jan; 76(2):442-9.
62. Papy-Garcia D1, Christophe M, Huynh MB, Fernando S, Ludmilla S, Sepulveda-Diaz JE, Raisman-Vozari R. *Glycosaminoglycans, protein aggregation and neurodegeneration*. Curr Protein Pept Sci. 2011 May;12(3):258-68.
63. McLaurin J, Franklin T, Zhang X, Deng J, Fraser PE. *Interactions of Alzheimer amyloid-beta peptides with glycosaminoglycans effects on fibril nucleation and growth*. Eur J Biochem. 1999 Dec;266(3):1101-10.
64. Mehra S, Ghosh D, Kumar R, Mondal M, Gadhe LG, Das S, Anoop A, Jha NN, Jacob RS, Chatterjee D, Ray S, Singh N, Kumar A, Maji SK. *Glycosaminoglycans have variable effects on α -synuclein aggregation and differentially affect the activities of the resulting amyloid fibrils*. J Biol Chem. 2018 Jun 29. pii: jbc.RA118.004267. doi: 10.1074/jbc.RA118.004267.
65. Clarisa M. Torres-Bugeau, César L. Ávila, Rita Raisman-Vozari, Dulce Papy-Garcia, Rosangela Itri, Leandro R. S. Barbosa, Leonardo M. Cortez, Valerie L. Sim and Rosana N. Chehín. *Characterization of heparin-induced glyceraldehyde-3-phosphate dehydrogenase early amyloid-like oligomers and their implication on α -synuclein aggregation*. J Biol Chem, [10.1074/jbc.M111.303503](https://doi.org/10.1074/jbc.M111.303503)
66. César L. Ávila, Clarisa M. Torres-Bugeau, Leandro R. S. Barbosa, Elisa Morandé Sales, Mohand O. Ouidja, Sergio B. Socías, M. Soledad Celej, Rita Raisman-Vozari,

- DulcePapy-Garcia, Rosangelaltri and Rosana N. Chehín. *Structural Characterization of Heparin-induced Glyceraldehyde-3-phosphate Dehydrogenase Protofibrils Preventing α -Synuclein Oligomeric Species Toxicity*. J BiolChem ., 10.1074/jbc.M113.544288.
67. Jinsha Huang, LijunHao, NianXiong, Xuebin Cao, Zhihou Liang, Shenggang Sun, Tao Wang. Involvement of glyceraldehyde-3-phosphate dehydrogenase in rotenone-induced cell apoptosis: Relevance to protein misfolding and aggregation Brain Res. 2009 Jul 7;1279:1-8. doi: 10.1016/j.brainres.2009.05.011.
68. Marta Barrachina, Esther Castaño, Esther Dalfó, Tamara Maes, Carlos Buesa, Isidro Ferrer. *Reduced ubiquitin C-terminal hydrolase-1 expression levels in dementia with Lewy bodies* Neurobiol Dis. 2006 May;22(2):265-73. Epub 2005 Dec 27 doi: 10.1016/j.nbd.2005.11.005
69. Berry MD, Boulton AA, *Glyceraldehyde-3-phosphate dehydrogenase and apoptosis* J Neurosci Res. 2000 Apr 15;60(2):150-4 doi: 10.1002/(SICI)1097-4547(20000415)60:2<150::AID-JNR3>3.0.CO;2-4
70. In-Su Kim, PalanivelGanesan, and Dong-Kug Choi *Cx43 Mediates Resistance against MPP⁺-Induced Apoptosis in SH-SY5Y Neuroblastoma Cells via Modulating the Mitochondrial Apoptosis Pathway* Int J Mol Sci. 2016 Nov; 17(11): 1819. doi: 10.3390/ijms17111819
71. Mark D. Berry *Glyceraldehyde-3-phosphate dehydrogenase as a target for small-molecule disease-modifying therapies in human neurodegenerative disorders* J Psychiatry Neurosci. 2004 Sep; 29(5): 337–345
72. Delunardo F, Soldati D, Bellisario V, Berry A, Camerini S, Crescenzi M, Alessandri C, Conti F, Ceccarelli F, Francia A, Valesini G, Cirulli F, Siracusano A, Siracusano A, Niolu C, Alex Rubino I, Ortona E, Margutti P *Anti-GAPDH Autoantibodies as a Pathogenic Determinant and Potential Biomarker of Neuropsychiatric Diseases* Arthritis Rheumatol. 2016 Nov;68(11):2708-2716. doi: 10.1002/art.39750. Epub 2016 Oct 9
73. Ho RC, Thiaghu C, Ong H, Lu Y, Ho CS, Tam WW, Zhang MW *A meta-analysis of serum and cerebrospinal fluid autoantibodies in neuropsychiatric systemic lupus erythematosus*. Autoimmun Rev. 2016 Feb;15(2):124-38. doi: 10.1016/j.autrev.2015.10.003. Epub 2015 Oct 23

74. Makhina T, Loers G, Schulze C, Ueberle B, Schachner M, Kleene R *Extracellular GAPDH binds to L1 and enhances neurite outgrowth*. Mol Cell Neurosci. 2009 Jun;41(2):206-18. doi: 10.1016/j.mcn.2009.02.010. Epub 2009 Mar 11
75. Laurén J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM *Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers* Nature. 2009 Feb 26;457(7233):1128-32. doi: 10.1038/nature07761
76. Hara MR, Thomas B, Cascio MB, Bae BI, Hester LD, Dawson VL, Dawson TM, Sawa A, Snyder SH *Neuroprotection by pharmacologic blockade of the GAPDH death cascade*. ProcNatlAcadSci U S A. 2006 Mar 7;103(10):3887-9. Epub 2006 Feb 27.
77. Stefanova N, Poewe W, Wenning GK *Rasagiline is neuroprotective in a transgenic model of multiple system atrophy*.Exp Neurol. 2008 Apr;210(2):421-7. doi: 10.1016/j.expneurol.2007.11.022. Epub 2007 Dec 4.
78. Gerlach M, Youdim MB, Riederer P *Pharmacology of selegiline*. Neurology. 1996 Dec;47(6 Suppl 3):S137-45
79. Hara MR, Snyder SH *Nitric oxide-GAPDH-Siah: a novel cell death cascade*. Cell MolNeurobiol. 2006 Jul-Aug;26(4-6):527-38. Epub 2006 Apr 22.
80. Makoto R. Hara, Bobby Thomas, Matthew B. Cascio, Byoung-Il Bae, Lynda D. Hester, Valina L. Dawson, Ted M. Dawson, Akira Sawa and Solomon H. Snyder *Neuroprotection by pharmacologic blockade of the GAPDH death cascade*ProcNatlAcadSci U S A. 2006 Mar 7; 103(10): 3887–3889 doi: 10.1073/pnas.0511321103
81. Jin-Ying Zhang, Fan Zhang, Chao-Qun Hong, Armando E. Giuliano, Xiao-Jiang Cui, Guang-Ji Zhou, Guo-Jun Zhang, and Yu-Kun Cui *Critical protein GAPDH and its regulatory mechanisms in cancer cells* Cancer Biol Med. 2015 Mar; 12(1): 10–22 doi: 10.7497/j.issn.2095-3941.2014.0019
82. Lazarev VF, Nikotina AD, Semenyuk PI, Evstafyeva DB, Mikhaylova ER, Muronetz VI, Shevtsov MA, Tolkacheva AV, Dobrodumov AV, Shavarda AL, Guzhova IV, Margulis BA. *Small molecules preventing GAPDH aggregation are therapeutically applicable in cell and rat models of oxidative stress*. Free RadicBiol Med. 2016 Mar;92:29-38. doi: 10.1016/j.freeradbiomed.2015.12.025. Epub 2015 Dec 31.
83. Gerszon J, Serafin E, Buczkowski A, Michlewska S, Bielnicki JA, Rodacka A. *Functional consequences of piceatannol binding to glyceraldehyde-3-phosphate dehydrogenase*.PLoS One. 2018 Jan 3;13(1):e0190656. doi: 10.1371/journal.pone.0190656. eCollection 2018.